REMARKS

Claims 7-10 and 12 - 24 are pending. Claim 11 has been canceled. New claims 18-24 are supported on page 7, lines 25 - 30; page 9, lines 32-33; page 12, lines 1-17; page 15, lines 17-23; page 16, lines 23-25 and lines 27-29; and page 34, lines 23-33.

A copy of the abstract provided with the preliminary amendment filed January 10, 2001 is enclosed herewith. Its entry is requested.

No new matter is added by this amendment.

Applicants note the examiner's statement with respect to the priority of the referenced phrase. While Applicants disagree with this statement on the basis that the terms used in the claims need not be found verbatim in the specification and the specification inherently supports this language at page 7, lines 25 to 34 and page 34, lines 17 to 21. However, the present amendment renders this rejection moot.

I. Claim Objections

Claims 7, 12 and 13 have been amended to correct minor clerical errors and consistent use of the abbreviations rAAV and AAV. This amendment does not alter the scope of the claims.

II. Rejections Under 35 USC §112, Second Paragraph

Claims 8, 9 and 12-17 have been rejected under 35 USC §112, second paragraph, as being indefinite.

Claim 8 has been amended to clarify that the transgene encodes the secretable protein. Claims 12 and 13 have been amended to clarify the meaning of the phrase describing the level of purity of the composition.

These amendments are believed to overcome the rejection with respect to the amended claims and the claims which depend therefrom. Withdrawal of this rejection is requested.

III. Double Patenting

Claims 7-17 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of US Patent No. 5,866,522 and provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9, 20, 21, 23, 25, 26, and 27 of co-pending Application no. 09/237,064. Claims 7-11 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-24 and 26-28 of co-pending application No. 09/242,977.

Applicants respectfully request that a reply to these rejections be permitted to be deferred until such time as the claims in this application are otherwise considered to be in condition for allowance.

The Invention

The observation by the inventors that intramuscular delivery of rAAV which is at least as free of contamination with helper virus as is obtained by subjecting the rAAV to four rounds of CsCl gradient centrifugation (and particularly, skeletal muscle) leads to highly efficient transduction of muscle fibers leading to stable and prolonged expression of transgene, which led to the present invention. Thus, it is the inventors' observation which enabled the present invention which delivers the selected secreted transgene (e.g., Factor IX) into muscle and achieves prolonged expression of Factor IX which is secreted and thus, found in the circulation for a prolonged period of time. Thus, the method of the invention is particularly well suited for providing prolonged expression of Factor IX in the circulation.

Further, this observation led to the finding that rAAV must be purified from helper adenovirus. This was essential to the present invention.

Further, having recognized and taught that a *minimum* level of purity of the rAAV was necessary, the inventors should not be limited to only the method of purifying away helper virus exemplified in the application. Nor should the inventors be limited to only that minimum level of purity which is taught to be necessary for the invention.

IV. Rejection under 35 USC §102(e)

Claims 7-11 have been rejected under 35 USC §102(e) as being anticipated by Podsakoff et al, US 5,858,351. The examiner has admitted in the §103 rejections that Podsakoff does not teach a rAAV vector composition comprising 5' ITR, nucleic acid sequence encoding ApoE, and 3' ITR, wherein the rAAV is at least as free of contamination with a helper virus as is obtained by subjecting the rAAV to four rounds of CsCl gradient centrifugation, as is taught by the present invention.

Podsakoff does not teach or suggest that administering a rAAV according to the present invention for efficient transduction of the muscle cells and prolonged transgene expression. Nor does Podsakoff teach or suggest that intramuscular delivery of a transgene encoding a secretable protein via such a method provides prolonged expression of the protein.

The claims have been amended to clarify the distinctions over the prior art. Withdrawal of this rejection is requested.

V. Rejections Under 35 USC §103

A. Claims 7-11 have been rejected under 35 USC §103(a) as being unpatentable over Podsakoff, in view of Kashyap, J. Clin. Invest., 96:1612-1620 (1995).

The defects in Podsakoff (discussed above) are not overcome by its combination with Kashyap. Kashyap refers to intravenous infusion of a recombinant adenovirus containing human apolipoprotein E (apoE) in apoE-deficient mice. Kashyap does not teach or suggest rAAV vectors. Nor does Kashyap teach intramuscular delivery using AAV vectors. In fact, given the apparent success of Kashyap with adenoviral vectors, there would be no motivation for one of skill in the art to deliver apoE via an alternative route or using other viral vectors.

For these reasons, even if combined, Podsakoff and Kashyap fail to suggest the present invention.

Reconsideration of this rejection is requested.

B. Claims 7-10 and 12-17 have been rejected under 35 USC §103(a) as being unpatentable over Podsakoff, in view of Fang, Hu Gene Therapy, 6:1039-1044 and Kay et al, US Patent 5,980,886.

Podsakoff describes rAAV-mediated delivery of erythropoietin. Fang describes adenoviral delivery of Factor IX cDNA in combination with an immunosuppressive agent cyclosporin A. Fang does not suggest intramuscular delivery of Factor IX. Kay teaches the use of a combination of retroviral and adenoviral vectors for transduction of hepatocytes by direct infusion into the portal vein. Kay does not teach or suggest delivering into the muscle for expression from muscle cells; nor are its teachings applicable thereto.

The combination of Fang and Kay with Podsakoff fails to supply these defects and in fact, teaches away from the present invention. Neither of the secondary references suggest the use of rAAV for any purpose, or the delivery of transgenes by intramuscular delivery.

The combination of these references fails to recognize the advantages of intramuscular delivery of a secretable protein via a rAAV which is at least as free of contamination with helper virus as is obtained by subjecting the rAAV to four rounds of CsCl gradient centrifugation. Absent this recognition, the combination of references fails to provide the motivation and reasonable expectation of success which are required elements to set forth a case of obviousness.

Reconsideration and withdrawal of the rejection is requested.

In view of these remarks, Applicants request favorable consideration of claims 7 - 24 presented with this amendment.

The Director of the U. S. Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to Deposit Account No. 08-3040.

Respectfully submitted,

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Appendix A
"Marked-up Version of Amended Claims"

7(Amended). A method for expressing a transgene in a skeletal muscle cell [in the absence of a cytotoxic immune response directed against the cell], comprising the step of introducing into the cell a recombinant adeno-associated virus (rAAV) comprising a transgene operably linked to sequences which control its expression, wherein the rAAV is [substantially] at least as free of contamination with a helper virus as is obtained by subjecting the rAAV to four rounds of cesium chloride gradient centrifugation and wherein the transgene is expressed in the cell.

8(Amended). The method according to claim 7, wherein the transgene [is] encodes a secretable protein.

9(Amended). The method according to claim 8, wherein the protein is selected from the group consisting of Factor IX, [ApoE,] β-interferon, insulin, erythropoietin, growth hormone, and parathyroid hormone.

10(Amended). The method according to claim 7, wherein the rAAV consists essentially of, from 5' to 3', 5' AAV [inverse] inverted terminal repeats (ITRs), a heterologous promoter, the transgene, a polyadenylation sequence, and 3' AAV ITRs.

12(Amended). A recombinant adeno-associated virus (AAV) comprising sequences encoding factor IX and regulatory control sequences which permit expression of factor IX in a cell, wherein the rAAV is at least as free of [level of contaminating] adenoviral helper virus as is [no greater than that] obtained by subjecting said recombinant AAV to four rounds of cesium chloride gradient centrifugation.

13(Amended). A composition comprising a physiologically compatible carrier and a recombinant adeno-associated virus (AAV) comprising sequences encoding factor IX and regulatory control sequences which permit expression of factor IX in a cell, wherein the rAAV is at least as free of [level of contaminating] adenoviral helper virus as is [no greater than that] obtained by subjecting said recombinant AAV to four rounds of cesium chloride gradient centrifugation.